Diphtheria.*

1. **Gravity of the Disease.**—Much study and a gradually widening experience have combined to make the diphtheria problem acute, at least to such investigators and administrators as take a scientific interest in medical treatment and community welfare. The problem may be stated thus: "Assuming that diphtheria," as Dr. Northup said in 1902, "is the disease of which we have the greatest knowledge as to causation, clinical symptoms, treatment and prevention, how comes it that while the case mortality may be generally decreasing, the total deaths registered from this disease during the past ten years show in some places an increase that is causing anxiety, if not alarm, and are still increasing?"

2. **Object of Present Inquiry.**—The present inquiry is undertaken with the object of finding, if possible, and setting forth some of the elements or factors that come into evidence in the search for a solution of the apparent medical paradox. In carrying it out the author has, as regards the disease, no proposition to prove, no thesis to propound or support, no elenchus to bring forward or argue, no cause to plead, no method of diagnosis to recommend, no line of treatment to urge, nothing novel to suggest. All that is attempted is a review of the facts and methods that must be considered in dealing with this dangerous disease. The contribution may be regarded as a study in the logic of medicine as applied to the problems of diphtheria, although, within the limits of space prescribed, an exhaustive examination of all the literature published on the various aspects of the subject is naturally out of the question.

3. **Desiderata in Investigations.**—Perhaps it is not sufficiently recognised that any investigations into the origin, character, treatment, and control of a disease of this nature entail two distinct tasks—firstly, the collecting of accurate and uniform statistics, and secondly, the drawing of logical inferences from them. The first should be essentially the work of medical men; the second is the business of expert statisticians. The most cursory examination of the published statistical data will show that a large proportion thereof is obviously untrustworthy. It would be unwise, however, in an investigation of this sort to pass by any statistics or class of statistics without careful examination and evaluation. In fact everything connected with the diagnosis, treatment, and control of diphtheria should be scrutinized in order to determine what is the real position of this disease at the present moment. For the purpose of this investigation the most likely sources of information have been explored and utilized.

4. **Definition of "Diphtheria."**—Probably no one would find much fault with the definition or description of "diphtheria" as an acute infectious disease accompanied by a membranous exudation on a mucous surface. In its typically recognized form it is so; but it must not therefore be inferred that the disease is as much differentiated from other diseases as an animal, plant, or metal is from other organisms or substances.

Forms of disease, corresponding very closely in character to diphtheria as defined or described, have been recognized and reported in medical literature for the past seventeen hundred years. These forms, however, were included in a general class of which neither the bounds nor the subdivisions were clearly defined. Down to the middle of the last century they were generally spoken of as croup, and were described under that heading. Croup, in the Encyclopædia Britannica, 1910, Vol. 7, p. 511, is said to be "a name formerly given to diseases characterized by distress in breathing accompanied by a metallic cough and some hoarseness of speech. It is now known that these symptoms are often associated with diphtheria (*q.v.*), spasmodic laryngitis (*q.v.*), and a third disease, spasmodic croup, to which the term is now alone applied."

The year 1858 might be selected as marking a new departure in the study of diphtheria, or even as a time of new manifestations of the spread, if not of the character, of the

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disease itself. In 1821 Bretonneau submitted to the French Academy of Medicine a treatise on this disease to which he had given the distinctive name of Le Diphthérite. This was one result of a general order issued by Napoleon regarding the investigation of the disease known by the name of croup. In the United Kingdom, the name diphtheria, was not adopted for a considerable time. Dr. Cheyne (1833) does not mention it; nor Marshall Hall (1837); nor Graves (1848); nor Thomas (ed. by Frampton, 1853); nor Copland (1858). Copland, however, in a comprehensive bibliography, mentions Bretonneau's name and contributions by him in the archives of medicine.

In January and February, 1859, "The Lancet Sanitary Commission Report on Diphtheria" was published in "The Lancet." Reference to the chief features of the disease, and the problems that had arisen in connexion with it is made in the first volume of the New Sydenham Society's "Annual Compendium of Scientific and Practical Medicine, 1860. Cyclopædias like Ziemssen's (1876) and Nothnagel's (1902) give good lists of literature on the subject; while Systems of Medicine, like Reynolds' (1866), with its article by William Squire, furnish instructive views on the subject at the dates of their publication. These, with clinical lectures, text-books of medicine, and contributions to medical magazines, supply the principal facts regarding the knowledge of the origin, symptoms, treatment and control of the disease down to the discovery of the bacillus, or the beginning of the Antitoxin Period.

It is generally recognized that certain requirements should be fulfilled if statistics are to yield trustworthy inferences. Among these are the following: (1) that reporters should be dealing with the same disease; (2) that medical practitioners should be reporting cases uniformly; (3) that registrars should be following the same method of recording primary and secondary causes of death; (4) that statisticians should be using the same methods in dealing with the notifications of cases and deaths.

Certain historical facts have to be noted, since the value for comparison of any series of statistics will depend largely on the period to which it relates. For example, it was not till 1855 that diphtheria was separated in English statistics from scarlet fever. The confusion of diphtheria with croup down to 1858 still influences statistics collected at the present time through inexactness in diagnosis and lack of uniformity in recording.

Is there an accepted definition or description of the disease called diphtheria? Does the word call up the same clinical or pathological picture to the minds of all physicians and pathologists and statisticians who employ it or who hear it?

Newsholme writing in 1889 on the use of statistics says: "There appears to be a fashion even in the names of diseases. In one doctor's practice nearly all the deaths from respiratory diseases will be returned as bronchitis, in another, perhaps as pneumonia." He then speaks of the effect of this in interpreting "national statistics," the errors tending to balance each other. With respect to the present subject he says:—"Perhaps there is no other case in which variations of nomenclature are so unfortunate as in diphtheria. A large proportion of the deaths due to this disease are doubtless returned as ulcerated throat, quinsy, laryngitis, membranous laryngitis, and especially croup. I have known cases certified as membranous laryngitis which were not entered in the Registrar-General's weekly reports as diphtheria, although they were acknowledged to be this by the practitioner in attendance, when inquiry was made by the local sanitary officials."

A perusal of the multifarious literature on the subject shows that in Europe, America, and Australia there is no stated accepted or recognized uniformity between the clinical and the statistical nomenclature of diphtheria.

A quotation has been given from Newsholme (1889) respecting difficulties arising from variations in nomenclature. But even where the same system of nomenclature is in use, there is room for fallacy on account of inexactness of notification.

Such inexactness, it may be noted, is not necessarily due to carelessness. It arises mainly from necessary limitations of clinical evidence even when all available means have been taken to ensure accuracy.

It might be thought that new methods of diagnosis would tend to increase the accuracy of statistics. Even if they should do so clinically in respect to a disease, there is still a statistical element to be considered. In the case of diphtheria there is a special source of error that may affect the case mortality and the general death rate. This arises from the practice, in some places, of notifying "non-clinical carriers" as sufferers from the disease, and including them in the statistics as "cases."

5. **Incidence of the Disease.**—(i) *General.* "The Lancet Sanitary Commission Report on Diphtheria," as abstracted in The Year Book of Medicine and Surgery for 1859, contained some facts showing that the disease is not solely dependent on the unhealthiness of the localities where it prevails; that wherever it has existed, among many varieties of its seat and symptoms, it has always preserved its distinctive characteristics and required the same kind of treatment; that so far no influence or condition has been detected to which the production of diphtheria can be ascribed; that it has prevailed at all seasons, and in all weathers, but that excessive alternations of temperature, or of the density of the air appeared to favour its development, and that its spread was believed to be occasioned in great measure by contagion.

In the same Year Book it is stated that the following conclusions are deducible from the table of cases published in the "British Medical Journal": Sex does not appear to influence the liability; age is positively influential, childhood and early youth being far more often attacked than more advanced age; hygienic conditions, occupation, food, and clothing, purity or impurity of air have not been shown to have much effect, the disease having occurred in many instances where the surrounding circumstances were favourable; our knowledge regarding meteorology extends no further than that the disease has prevailed during the most opposite states of the weather; though the disease may be communicated by contagion sometimes, that is not the usual mode by which it spreads.

These statements, formulated by the editors, Dr. Harley, Dr. Handfield Jones, Mr. Hulke, Dr. Graily Hewitt, and Dr. Odling, may be accepted as setting forth trustworthy observations regarding the characteristics of diphtheria at that date.

(ii) *Locality.* Both the reports mentioned above agree as to the general features of the epidemic as it occurred in various localities at that time. Locality did not appear to have much effect on its manifestations. The subject of locality has, however, acquired a new significance in view of the changes, geographical and social, that have occurred since then, and that alter the whole aspect of the incidence and spread of the disease.

In the Encyclopædia Medica (1916) Dr. Goodall writes: "Before the appearance of Newsholme's work, it has been shown that for England and Wales one of the most striking features with respect to the prevalence of diphtheria was that, whereas up to 1880 the disease was incident upon the rural to a greater extent than upon the urban population, since that date the reverse has been the case; there has been an increase both in rural and urban diphtheria, but the urban incidence has risen to a much higher degree than the rural. London has especially suffered. Newsholme's observations show that this increase in urban diphtheria is not confined to England and Wales, but has also occurred in countries so widely separated as the United States, Japan, and South Australia. It is reasonable to suppose that the wonderful improvements effected during recent years in our means of transit have had no small share in contributing to this increase."

Squire, in Reynold's System of Medicine (1866), writes: "It is somewhat remarkable that though diphtheria existed both in India and California, we have no history of any outbreak of it in Australia until 1859, when Mr. James Moore (Australian Medical Journal, July, 1859) records nine deaths from this cause, and the occurrence of 275 cases at the same time in New Norfolk, Tasmania. This part of the world is perhaps more exclusively in communication with England than any other. The appearance of the disease there is not until after it had attained in this country to its full epidemic development." In the same year cases elsewhere in Australia are reported in the local newspapers.

In more recent times Cormack (Quain's Dictionary of Medicine, 1890) remarks: "In cold damp weather the mortality is greatest;" and he adds, "The medical constitution of the season, and the character of an epidemic greatly influence prognosis."

(iii) *Cyclical Changes.* Newsholme (Vital Statistics, p. 119) says: "The fact that certain diseases, especially those of an infectious character, recur after an interval of years, shows that, apart from the influence of the season of the year, there are periods of change which require for their completion a series of years. Mr. Netten Radcliffe has drawn attention to the fact that the law of periodicity of epidemic and pandemic diseases is not yet determined. Two factors appear to be at work: (1) the influence of an accumulation of susceptible persons in the intervals between two epidemics of the

same disease: and (2) certain extraneous conditions which appear to be operative in determining the periodicity, but about which little or nothing is known." He refers to Radcliffe's inclusion of "the great development of diphtheria within the last thirty years" under the second factor.

(iv) *Hygienic Conditions.* Chapin gives a comparative study on this subject. He states (Sources and Modes of Infection) that "during the decade 1890–1899, Boston had the best sanitary administration of any of the large cities, though New York stood high. The death rate from diphtheria in both cities was 84 per 100,000 living, from scarlet fever –25 for Boston, and 33 for New York. Certainly neither Chicago nor Cincinnati enforced such rigorous measures, yet the rates in these two cities were 72 and 71 for diphtheria and 17 and 7 for scarlet fever. Among the smaller Massachusetts cities Fall River has usually had a rather inefficient health service, and little hospitalization, yet the death rate from diphtheria was 21 and from scarlet fever 15 per 100,000 living, while in Worcester the figures were 48 and 8, and this notwithstanding the fact that in Fall River the proportion of children is much greater than in most American cities, and that the population is exceptionally ignorant as measured by illiteracy. Worcester has had a contagious-diseases hospital since 1897, and has removed to it in some years as high as 63 per cent. of its diphtheria cases. In general, Worcester secures an excellent registration of cases and consequent isolation. Nevertheless Worcester has recently had, notwithstanding its increasing hospitalization and good home isolation, a severe outbreak of the disease. It seems a fair assumption that some factor much more important than the recognized causes of the disease has been at work in Worcester. If it were not so, the reported cases of the disease should not have risen from 132 in 1905 to 1,178 in 1907."

(v) *Social Conditions.* According to the Year Book, 1859, Lancet Report, "The fatality of epidemic sore throat and diphtheria appears to have been half as great again in the middle as in the lower ranks of society when a comparison is made with the mortality arising out of diseases of all kinds." In the same year, the British Medical Journal, speaking of Dr. T. H. Smith's experiences, says: "His remarks are in the main confirmatory of those of other observers. He testifies to the remarkable exemption of the pauper class of patients, to the distinctness of the disease from scarlatina, and to the absence of any peculiar localization of the disease in the haunts of fever and cholera." In Germany it was shown that the years of increase down to 1912 were partially times of crises and high prices, and the scarcity of habitations, a specially important factor, was on the increase, chiefly as regards small dwellings.

(vi) *Age and Sex.* The following table, from Allbutt's System of Medicine, is compiled from the County of London Records of Diphtheria for ten years ending 1903. It shows the age and sex incidence.

AGE AND SEX INCIDENCE OF DIPHTHERIA—COUNTY OF LONDON, DECENNIUM ENDING 1903.

Ages.	Cases Notified.		Deaths.		Case Rate per 1,000 Living.		Percentage Fatality.	
	Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.
All Ages	53,671	63,890	9,059	9,592	2.5	2.8	16.9	15.0
Under 1 year ..	1,477	1,128	630	528	2.8	2.2	42.7	46.8
1– 2 years ..	4,044	3,561	1,571	1,445	8.4	7.4	38.8	40.6
2– 3 ,, ..	5,219	4,777	1,537	1,488	11.3	10.4	29.5	31.2
3– 4 ,, ..	6,264	6,144	1,481	1,469	13.9	13.7	23.6	23.9
4– 5 ,, ..	6,180	6,473	1,188	1,326	14.0	14.7	19.2	20.5
5–10 ,, ..	16,854	20,328	2,110	2,692	8.1	9.7	12.5	13.2
10–15 ,, ..	5,865	7,753	309	341	2.9	3.8	5.3	4.4
15–20 ,, ..	2,766	3,812	73	81	1.4	1.7	2.6	2.1
20–25 ,, ..	1,802	3,193	43	39	0.8	1.2	2.4	1.2
25–35 ,, ..	2,099	4,287	43	77	0.6	1.0	2.0	1.8
35–45 ,, ..	739	1,587	32	43	0.3	0.5	4.3	2.7
45–55 ,, ..	235	603	24	23	0.1	0.3	10.2	3.8
Above 55,, ..	127	244	18	40	0.1	0.1	14.2	16.4

Dr. Tatham says, "This table indicates that, according to London experience, which extends to 117,561 cases within a period of ten years, the incidence of diphtheria is mainly limited to the period of childhood, the ages from two years to five being those most liable to attack. Comparatively few cases occur in the first year of life, but the fatality among infants attacked at that age is excessively high. In proportion to population, the notified cases are comparatively few in number after the tenth year of life, and the case fatality is below the mean except among women above the age of 55 years."

(vii) *Susceptibility.* The subject of susceptibility in races apparently has not been intensively studied, but it would appear on a cursory review of statistics of mortality that the negro in America is less susceptible than the white. The effect of previous diseases, as giving immunity or predisposition, does not appear to have been the subject of close inquiry. In the Year Book, 1859, mention is made of 47 cases, 12 of which had suffered previously from scarlet fever.

(viii) *Prevalence.* The testimony to the increased prevalence of diphtheria in almost all countries is universal. It is the most urgent problem of the present day as regards the disease.

6. **Type and Epidemic Constitution.**—(i) *General.* In 1918, when influenza was reported in various parts of the world, there was not a little speculation as to whether it was a new disease, requiring a new name and new methods of treatment and control, or whether it was one of the several protean forms that had been studied in time past, and was to be regarded as influenza showing a particular type or epidemic constitution that had been observed in former outbreaks. Some consider the question still debatable.

(ii) *Changes in Type.* An epidemic of a communicable or infectious disease in one place may show, for example, an alteration in age-incidence when compared with an epidemic of the same disease at a former time. Again, there may be a difference in its extent, its prevalence, or its virulence, these last two characters not being necessarily concomitant.

The term "epidemic constitution" is defined and illustrated by Latham at considerable length. The name, he says, "indicated nothing of the nature of the thing itself; but it acknowledged a reality and a power." In the course of his exposition he says: "Behold, for a season mankind in various places and circumstances require a treatment for their diseases contradictory to the experience of former times. Then wait for a season, and behold, mankind, in the same places, and in the same external circumstances, will require a treatment for the same diseases contradictory to the experience of the present times. But neither now, nor formerly, nor hereafter, will there be found in the vital being of men themselves, in their places or circumstances, anything to reconcile the contradictions or at all explain them." Again he says: "Let present indications be justly chosen, and fulfilled according to a fit measure, and then the treatment which they suggest, while it is variable at different times, will be at all times uniform in its success."

Sydenham, who devoted a large amount of study to this subject, pointed out that acute diseases showed a long period of evolution, with a rise, a decline and a fall, extending over centuries and, at the same time, seasonal variations with waves measured in months so that their character and reaction to treatment varied at intervals.

In recent times the general subject of type has been discussed by Sir Humphry Rolleston under the heading "The Change of Type of Disease." He says: "At the present time no one doubts that certain diseases have shown changes of type; scarlet fever is universally recognized to have become much milder." Brownlee finds that though there is not any evidence that the amount of scarlet fever (or the infectivity of the causal agent) is less now than in the latter half of the last century, the mortality (or the virulence of the organism) has greatly fallen. Pneumonia is another example of a disease in which the virulence, as shown by the mortality, has increased, and the type of the disease has, since the reappearance of influenza in 1889–1890, undergone some change, the disseminated form being common and the frank lobar pneumonia less frequent. The seasonal variation of type was shown in a well-marked degree by the two waves of influenza in the spring and autumn of 1918, the high rate of thoracic complications and of mortality in the second wave being associated with *streptococcus hemolyticus* and the *pneumococcus.*

"In the Royal Navy the spring wave of influenza was accompanied by 0.4 per cent. of complications and 0.03 per cent. mortality, whereas in the autumn wave the incidence of complications was 6.8 per cent. and of deaths 2.8 per cent."

The subject of epidemic constitution came into prominence at the time when diphtheria was recognized in England as a distinct disease. In the Sydenham Society's Year Book, 1859, a summary is given of an article by Henry Kennedy. He states it "as a patent fact, that both animal and vegetable life is subject at times to epidemic influences, which at one period raise, and at another period depress, the standard of health. These determine the so-called "constitutio anni." These were carefully noted by the older writers, and their practice shaped accordingly." . . . . . He also strongly insists on the need for a discriminating therapeutism, affirming that no single plan can possibly meet the ever-varying shades of disease, some inflammations requiring wine (alone), some mercury, some bleeding, general or local, or both." The view of Dr. Adolf Gottstein on this subject is that the waves of diphtheria prevalence are attributable to rhythmical variations in power of resistance of successive generations, the weeding out of the less resistant being accomplished to different extents at different times.

Since 1859 much has been written on the subject of change of type or epidemic constitution of diphtheria, and not a little speculation has been hazarded, and investigation made as to the causes of such changes.

(iii) *Bacteriological Causes.* Bacteriological causes have been suggested for change of type. It is said that bacteria may vary in pathogenicity from internal causes, and that these may give rise to such cyclical recurrences of disease as have been observed in measles and influenza. Again, it is suggested that change of type may be due to external causes, such as food, alcohol, climatic conditions, overcrowding, overwork, changes in resistance of the patients. These have been discussed at some length by Rolleston and others. In this connexion the difference between prevalence and virulence has to be noted. It has been suggested that fluctuations in prevalence may illustrate changes in the life-history of the disease organism, while mortality may express the accident of its manifestation in surroundings unfavourable to the person attacked.

(iv) *Influence of Urban and Rural Distribution of Population.* In the case of diphtheria it would appear that the variation in relative proportions in the urban and rural populations may have had a pronounced effect on the incidence, if not also on the virulence, of the disease in recent times. Formerly it was essentially a rural disease, now it is becoming a characteristically urban disease throughout many, if not most, parts of the world.

(v) *Necessity for Separate Individual Diagnosis.* It has been said that although cases may be regarded as belonging to types, each case requires its special study, speaks its proper language. The laity have considered this in connexion with treatment. Amiel says: "Why do doctors so often make mistakes? Because they are not sufficiently individual in their diagnoses or their treatment. They class a sick man under some given department of their nosology, whereas every invalid is really a special case, a unique example. How is it possible that so coarse a method of sifting should produce judicious therapeutics? Every illness is a factor simple or complex, which is multiplied by a second factor, invariably complex—the individual, that is to say, who is suffering from it—so that the result is a special problem, demanding a special solution, the more so the greater the remoteness of the patient from childhood or from country life."

(vi) *Quantitative and Qualitative Observation.* If there be such types, or epidemic constitutions, in time and place, then in proportion as an investigator takes account of them, he will make his observations and frame his experiments quantitatively and qualitatively so as to yield trustworthy results, and thus to give indications for further research and treatment.

7. **Diagnosis.**—Correct diagnosis of any disease is obviously of paramount importance as affecting the validity of inferences drawn from statistics of cases or deaths connected therewith. Before considering diphtheria, it may be well to examine the subject of diagnosis in general, in view of the circumstance that it is not studied to the extent it deserves by writers on public health. The following is extracted from "Vital Statistics, a Discussion of What They Are and Their Uses in Public Health Administration," by

John W. Trask, Assistant Surveyor-General, United States Public Health Service, Washington: "Perhaps the most common error entering into death registration, and therefore into mortality statistics, is in connexion with the statement of cause of death. Aside from the fact that in the instances in which it has been impossible for the attending physician to feel reasonably certain as to the nature of the terminal illness, a cause of death is nevertheless usually stated in the certificate, and also the fact that at times the physician knowing the nature of the illness may, in the belief that he is shielding the family from odium, or because of their whim, intentionally state an erroneous cause of death, there still remain the many unavoidable errors of mistaken diagnosis. Just how great a factor this last may be it is difficult to estimate. However, the findings of Dr. Richard C. Cabot give at least a hint of its possible importance, and the extent to which it may affect that part of mortality statistics relating to causes of death. [In a study of 3,000 autopsies with regard to the relation of the actual cause of death as found post-mortem to the clinical diagnosis, Cabot found that the percentage of correct diagnoses in various diseases ranged from as low as 16 in acute nephritis to 95 in diabetes mellitus.]

The cases studied were hospital cases under conditions assumed to be favourable to correct diagnosis. It is quite safe to assume that in medical practice at large the percentages of correct diagnosis would be found lower than those found by Cabot."

Diphtheria did not come within the scope of Dr. Cabot's inquiry. It is difficult to estimate what the percentage would have been in respect to this in pre-Klebs-Löffler bacillary days. And yet all statistics of diphtheria of those days have to be considered in the light of accuracy of diagnosis when employed for the purposes of comparison.

When the antitoxin period is reached the question becomes still more important. In an article by Dr. Armand Ruffer, in The Medical Annual for 1895, the following occurs: "Before we come to the results which have been obtained by this method, it is necessary to point out one cause of error which affects all statistics of diphtheria. One finds that a great many cases which are certified as diphtheria and admitted into hospitals, are, as a matter of fact, not diphtheria at all, as the specific bacillus cannot be found in them. Such cases nearly always recover, and if one were to include them in the statistics of diphtheria cases treated by serum, the mortality would appear to be far too low. It is necessary, therefore, before the value of treatment can be established, to examine each case so treated for the diphtheria bacillus. This should be systematically carried out when the antitoxin treatment is being tried."

8. **Treatment.**—(i) *General.* Too much stress cannot be laid on the necessity for early identification and treatment of the disease. It has been noted that diphtheria differs in certain respects from other diseases like scarlet fever, measles, and mumps, which run a fairly normal course and tend to recovery of the patient. With diphtheria, in addition to the general or constitutional symptoms, there is often a local condition of the throat that makes feeding and breathing extremely difficult, besides acting as a factory for the making and supplying of poisons to the system. It is this local lesion that is regarded as the crux in various forms of treatment, and that may form one of the most important factors in the spread of the disease. In the use of stimulants in this disease Jacobi's observations are worthy of note. He says: "A mild invasion does not assure a mild course. Never has a 'possible superfluous' tonic or stimulant done harm in diphtheria, but many a case has a sad termination because of a sudden change in the character of the disease putting the bright hopes of the physician to shame."

The literature on the subject of local applications in past times is very considerable. It was recognized that measures that could destroy the presumed infective material locally without harmful results were of the greatest use. Modern measures, it has been said, are not intended to remove the diphtheritic membranes but only to destroy the bacillus and to prevent the production of toxins. If they help to do this they are worthy of consideration, much more so if they do it effectively. A good deal of study has been devoted to the technique of local applications. It is difficult to obtain a substance that is effective in the short time allowed for its application, while the difficulty of applying in the case of young children is sometimes very great, and the patients become agitated and exhausted in their struggles to resist. Among the approved substances are potassium permanganate, boric acid, corrosive sublimate alone or combined with ichthyol, sozodol with milk of sulphur. Löffler used a solution of menthol, toluol, creoline, metacresol, or perchloride of iron, and recorded 96 cases treated without a death. Trousseau (1867)

tells of his inquiries into a remarkable stopping of an epidemic that was characterized by a frightful mortality. He found through the parish priest that the cessation was due to an old woman's treatment. Trousseau witnessed and verified the results, and found that the change was brought about by the use of a gargle of alum and vinegar in water. The mode of treatment was thereupon printed, published, and sent to the different communes. Bretonneau adopted it, and it was used by all physicians in the treatment of diphtheria. Many other substances have been used, from the time of Aretaeus downwards; and it would appear that a large part of their efficacy depended on the manner of application and the skill of the attendant.

(ii) *Antitoxin.* (*a*) *Mouth Administration.* Hewlett, in 1902, recorded experiments showing that administration by the mouth or rectum was valueless. His conclusions were founded on the fact that such administration to rabbits and guinea-pigs did not prevent these animals from succumbing within a short time to lethal doses of toxins administered subcutaneously, whereas the subcutaneous injection of antitoxin acted as a preventive or antidote. This, it must be noted, assumed that absorption from the alimentary tract would be the same in human beings as in rodents. Pilcher and Paton had great confidence in the oral administration of antitoxin. King and McLintock immunized animals with diphtheria toxins orally administered, by taking precautionary measures against the action of the gastric juice. In respect to clinical evidence, it is stated that at the East London Hospital for Children all serums were given by the mouth, except in cases of very urgent laryngeal diphtheria, when it was given subcutaneously. In " Osler and McCrae's Modern Medicine " it is stated : " Oral administration is too slow and its effects too uncertain for practical use."

(*b*) *Efficacy of Serum.* From the first introduction of antitoxin, there has been much testimony both in favour of and against its use, and a relatively less amount of critical examination of the arguments adduced in support of conclusions.

Behring, the inventor, was severely criticized by Hansemann, but it has been stated that the dispute in Germany was much influenced by personal animosities. Dr. Rupp criticized the statistics of Monte and Kretz, and concluded that they did not satisfactorily prove the efficacy of antitoxin. In London, Lennox Browne treated two series of 100 cases each, the one with, the other without, antitoxin, and although the series treated with antitoxin showed an apparent reduction in mortality as compared with the other, from a careful analysis he believed that this was apparent and not real, and that grave complications, such as anuria, nephritis, and cardiac failure were increased by the use of the serum. Gayton, of the North-Western Fever Hospital, considered that although the mortality in his cases was somewhat lowered, this was due to a less virulent form of the disease rather than to the treatment. He summed up his view thus : " Those cases that under the old treatment would probably have died were still fatal under the new, those which might get better recovered in about the same proportion, whilst the mild cases improved no more rapidly—indeed, rather the contrary."

Behring himself was modest in his claims for the efficacy of antitoxin. He said : " I am now definitely of opinion that under suitable treatment with my remedy, the mortality from diphtheria may be reduced to under 5 per cent. if the serum be used in good time—that is, before the third day of illness."

At the present time, the use of antitoxin is widespread and strongly recommended, statistics being used as conclusive arguments for its employment in practically all known or suspected cases of diphtheria.

(*c*) *Dosage.* Practice has been extremely varied both in regard to the amount of the dose, and the length of the intervals between the doses. The dose has varied from less than 600 units to 9,000 units. In one recorded case a child of 3 years received 225,000 units. Some physicians gave 1,000 units for an average dose. D'Agnanno ascribes the different percentages given by various observers to : (1) The period of the disease at which the injection is practised ; (2) The quantity of the serum used ; (3) Local treatment ; (4) The varying proportion of faucial and laryngeal cases. Commenting on this the

recorder in "The Medical Annual for 1898" said: "But he omits a very important point, that of numbers, for to get a percentage which will be practically correct, we need at least thirty-three thousand cases." In one administration area the Health Department distributed 27,000 units for each case reported. So far, there does not appear to be any recognized dosage table for age, sex, general condition, type of disease, or complications.

(*d*) *Time of Administration.* All practitioners who use antitoxin urge that it should be administered at the earliest indications of the presence of the disease; many employ it if there is reason to suspect that the disease may possibly be present.

(*e*) *Sequelæ.* Sequelæ of antitoxin treatment are varied and frequent. In some statistical records abscesses were noted at the seat of puncture in 1.2 per cent. of cases; joint pains in 6.5 per cent.; pyrexia with or without rash or pain in 19.8 per cent.; urticarial, erythematous, or scarlatinal rashes in 35.2 per cent.; albuminuria in from 53 to 24 per cent.; nephritis in from 1.2 to 0.5 per cent.; lobular pneumonia in from 2.5 to 1.6 per cent.; and various paralyses in from 2.3 to 13.2 per cent. Other statistics would suggest that complications are rare. In the case of albuminuria and nephritis it would not be possible, without a large number of control cases, to say what effects might be due to the disease and what to the treatment. In the Chicago Hospital Statistics it is recorded that cervical adenitis was noted in 62 per cent.; paralysis, usually of the muscles of deglutition, in 9 per cent., not including those in which the heart was involved; and 5 per cent. suffered from otitis media. Of 834 deaths, 137 were due to bronchopneumonia, and 78 to myocarditis.

(*f*) *Anaphylaxis.* On this subject of serum treatment a general statement by Dr. Rendle Short demands consideration. In his book, The New Physiology in Surgical and General Practice (1922), he writes: "It is well known that when certain proteins are injected into an animal's blood-stream, so far from antibodies being formed, there may be an increased sensitiveness developed, so that a second injection months or years afterwards may produce severe or even fatal symptoms. A few cases are on record in which second injections of horse-serum containing diphtheria or other antitoxin have caused most alarming illness or death. Now that so many men who were wounded in the war and given a dose of antitetanic serum are about in the community, it is possible that there may be trouble one day when one of them is given diphtheria antitoxin or some other preparation of horse-serum protein. It is also well known that if the second dose is given within a week, this sensitization (anaphylaxis) does not occur."

9. **Results of Treatment.**—(i) *General.* Reference has been made above to the results when the treatment is begun at an early stage of the disease. Statistics dealing with this will be considered later. Other circumstances influencing results will now be considered.

(ii) *Ballard's Researches.* Ballard in 1858–9 studied the conditions pertaining to eighty fatal cases in the parish of Islington. He classified them in respect to their truly diphtheritic character: "Class I., cases in which he obtained satisfactory evidence of the presence of the true diphtheritic exudation upon the throat, or in which he saw it himself during life. Class II., cases which were certified as deaths from diphtheria by the medical attendant, but in which he obtained no particulars of the appearance of the throat. Class III., cases in which he was assured by the medical attendant that the exudation was absent. Class I. consists of 31 males, 25 females—total 56. Class II. of 4 males, 9 females—total 13. Class III. of 6 males, 5 females—total 11. General totals—41 males, 39 females. As to age, 5 deaths occurred under 1 year; 12 from 1 to 2; 11 from 2 to 3; 13 from 3 to 4; 7 from 4 to 5; 19 from 5 to 10; 7 from 10 to 20; 6 at 20 and upwards. As to the duration of the disease, in four infants under one year, the main duration was four days; at each of the other ages, it was from nine to eleven days. As to the modes of death, and the period at which they prevailed, it appears from Dr. Ballard's tables that 'the danger from which a fatal result is mainly to be apprehended in the course of the first week of the disease is extension of the disease to the upper part of the air passages, with consequent asphyxia The sudden deaths in this week are probably due to the same cause, giving rise to spasmodic closure of the glottis. As the malady advances into the second week, the chances of death from this

cause are only equal to those from the general prostration of the vital powers. In the third and fourth weeks, the latter is the condition mostly to be dreaded; the sudden deaths at this time being probably due to syncope." As to the social position of the patients, it appears that "the fatality of epidemic sore-throat and diphtheria appears to have been half again as great in the middle as in the lower ranks of society, when a comparison is made with the mortality arising out of diseases of all kinds'."

The number dealt with is relatively small, and the total number of patients is not stated, but the results are interesting as showing that the ratio of the first five to the second five years' deaths was 48 to 19 at that time—that 60 per cent. were under 5, and 23.75 per cent. between 5 and 10.

(iii) *London Returns, 1892 to 1912.* The London notifications of cases show that for 1892 to 1912, about one-third of the cases are under the age of 5 years, and about another third between the ages of 5 and 10; also that age has a marked influence on case mortality.

(iv) *Returns for Scotland, 1860 to 1911.* The mortality rates for the population of Scotland per 10,000 for various triennial periods since 1860 are shown in the following table:—

DIPHTHERIA AND CROUP.—MORTALITY RATES PER 10,000 LIVING, SCOTLAND, 1860 to 1911.

Ages.	1860-2.	1870-2.	1880-2.	1890-2.	1900-2.	1909-11.
Under 5 years	33.3	31.5	25.7	22.3	12.2	11.9
Under 10 years	7.9	7.5	6.6	6.4	3.3	4.5
Under 15 years	1.8	1.1	1.2	1.0	.7	.8
15 years and over	.4	.3	.2	.2	.1	.1
All Ages ..	5.9	5.5	4.6	3.8	2.0	2.0

It will be observed that the decrease for "all ages" in the first four periods was becoming more marked, that from the fourth to the fifth it was strongly marked, but that from the fifth to the sixth there was no decrease. The compiler notes that a third element has to be considered, viz., a change in the age-distribution of attacks which has accompanied the increased prevalence which he has been considering. He shows that with the increasing prevalence there has been a relatively greater invasion of the age-period 5 to 15. This is an age of relatively fewer deaths.

The significance of this table may be better appreciated when one considers that notification of diphtheria was not universal until 1899. Then, under radically changed circumstances, an active health propaganda made its effects evident in urban and rural communities alike. It is obvious that no accurate estimate is possible regarding the case mortality in diphtheria previous to the adoption of universal and uniform notification of the disease.

To control infectious diseases effectively, it is necessary (*a*) to detect every case in the earliest stage at the earliest possible moment; (*b*) to isolate the sick from the well and to keep them isolated; (*c*) to isolate, under observation, persons who may be contacts of the sick. Isolation consists in establishing a "biological barrier," which need not be geographical or physical. The prime requisite in all procedure, for control, is notification to the administrative authorities. Such notification was optional on the part of local authorities in Great Britain (with a certain provision for compulsory

notification in Scotland) from 1889 to 1899, when it was made compulsory and universal. "Hospitalization" of infectious diseases is of recent date in the United Kingdom and most other countries. Its specific adjuncts are speedy and accurate bacteriological diagnosis; safe and ready transport, admission to hospital at all hours and constant supervision by trained attendants; district or hospital nurses for visiting "out-door" cases; inspectors trained and certificated in disinfection and other sanitary administration. Except in a few favoured localities, these means were not available for the treatment or control of infectious diseases before antitoxin times. The Isolation Hospitals Acts in England date from 1893 and 1901.

(v) *The Co-efficient of Expectancy.* Sir Malcolm Morris in "The Practitioner" in 1895 said: "The results so far achieved by the antitoxin treatment of diphtheria appear to me to give solid ground for the hope that at last a real antidote to this bane of child life has been discovered. Of course, in estimating the value of any new remedy which excites the enthusiasm of the profession, it is always well to leave what dressmakers, I believe, call a 'margin for shrinkage.' The weak point in the new treatment, to my mind, is that it is too successful; its effects are painted in colours too brilliant not to fade a little by and by. One of the lessons which the philosophy of medical history teaches is that a *new remedy always cures.*"

Some years ago a writer in "Le Monde Médical" said: "Every new method of treating chronic pulmonary tuberculosis, provided it be harmless, always yields satisfactory results. This is an axiom which is absolutely true, one which I should like to see inscribed in large letters on the first page of every new work on phthisiotherapy because, if it be not borne in mind, it renders it impossible to gauge the value of any new mode of dealing with this disease." The co-efficient of expectancy can in some cases be estimated in respect to its effects on physician, patient, friends and nurses.

In other cases it may be difficult to gauge the immediate and the remote effects of expectation and confidence on the treatment of patients and the control of disease unless experimental investigation is made on an extensive scale and according to the canons of the logic of medicine.

(vi) *Results on Convalescence.* The general statement has been made by Dr. C. H. Roger that statistics clearly establish that, under the antitoxin medication, the period of convalescence has been considerably reduced. There seems, however, to be a lack, if not a complete absence, of statistics bearing on this subject.

10. **Interpretation of Results.**—(i) *General.* Much of the "advance" of modern times, many of the recent errors in general medicine, abandoned or still in vogue, have resulted from inferences drawn from some assumed scientific principle or solitary fact and applied to modes of treatment.

In 1864 Dr. Barclay delivered the Lumleian Lectures to the College of Physicians on "Medical Errors: Fallacies Connected with the Application of the Inductive Method of Reasoning to the Science of Medicine." Referring to what may be called the variable causes influencing the results of an attack of disease he says: "First, before the attack: the sex, age, and social position of the individual; his previous state of health, including early constitution, acquired habit, and the effect of the relative amount and purity of food and air; his actual condition, whether suffering from any minor ailment (to say nothing of major complications, which may be excluded), from actual privation or cold, or from any recent excess. Secondly, as regards the seizure itself: its immediate cause; its intensity; the rapidity of its development and progress; and the extent to which the special organ attacked is affected by it. Thirdly, the circumstances external to the patient influencing the progress of the disorder: such as his home; the means at his command; the friends that surround him, ignorant or well-informed; his nurse and his food, including stimulants, as well as other nourishment; the skill of his medical attendant; and the judgment with which other subsidiary remedies are employed; if necessary, the influence which the conditions

calling for their employment exercise over the disease, no less than the remedies themselves; and, perhaps more than anything else, the discretion with which the amount of stimulants is strictly limited to the exigencies of the particular case. Lastly: the wonderful and inexplicable influence of mind over body, the condition of hope or fear, of quiet confidence or restless anxiety. This list is far within the limits of all possible circumstances affecting the result, because it is intended to be general, and to include those only which are undoubtedly of sufficient power to lead to a fatal result, or a lingering convalescence. I need not, therefore, go into a detailed examination of them individually. The list is a long one, and each circumstance mentioned presents several varieties; so that if it be required to neutralize their influence completely, the number of cases selected must be such as shall fairly represent all possible conditions in these respects, and afford a true comparison between the two series. For whatever the number needed, it must be borne in mind that it is essentially a comparison, and that a series of hundreds of cases which seemed to do well under a particular mode of treatment is valueless, because perchance a similar series in which the remedy was not administered might have done better." Elsewhere he says: "The statistics of our large hospitals collected under ever-varying circumstances as to the antecedents of the patient, the nature of the attack, and the pet prejudices and customs of the physician by whom he is treated, amounting as they soon would do to a large number, would afford a basis of calculation on such points of very considerable value, because the chances of error would, from the nature of the inquiry, be comparatively small."

Sir Henry Holland says: "Through medical statistics lies the most secure path in the philosophy of medicine." As an illustration of the practical application of statistics he says: "A question may be started whether it is possible to reach any sound conclusion without including in the average those cases where there has been no treatment at all. If the tables show a mortality of 75 per cent. under one method of treatment, and only 60 per cent. under another, this does not logically prove the latter to be beneficial, but merely gives evidence that the former is injurious."

It may be well to illustrate the present subject by applying some of the recognized tests of medical logic to the statistics accepted as more or less authoritative in order to see how far the statements of facts, *i.e.*, the figures, and the inferences drawn from them, *i.e.*, the conclusions, conform with the canons of logic—that is, to find out what information the statistics are capable of supplying.

When Balfour found that Skoda's patients in Vienna were left to sink or swim without phlebotomy, while others at the same time, and in the same city, and under similar conditions, were being treated *secundum artem* by profuse blood-letting, he was witnessing an investigation according to the logical "Method of Difference." When patients in Edinburgh were being treated, one set by profuse bleedings and another in similar conditions at the same time by varying degrees of small bleedings, the investigation was being made by the "Method of Concomitant Variations."

According to Jacobi, the doctors in Vermont in 1862 made a complete and wholesale reversal of the treatment during an epidemic of diphtheria, and the death rate fell from 90 per cent. to 10 per cent. This was an application of the "Method of Difference"—provided that, in the meantime, no unrecorded or unnoticed seasonal change had occurred, or other varying element had complicated the problem. As a rule, few investigations can be made under such favourable conditions, *i.e.*, conditions so definite as to yield accurate comparisons and trustworthy results.

From what has been said and quoted above, it will be seen that the problem of diphtheria is a very complex one, involving many factors, and demanding for its investigation extensive series of accurate medical observations coupled with expert statistical analysis in order to reach even a fair amount of probability in respect to the influence of any given or supposed single factor.

(ii) *Influence of Diagnosis.* In dealing with questions of the incidence, treatment, and case mortality of any disease, the prime essential is a certainty that all the facts and figures that are being studied refer to the subject of investigation, in other words, the first requisite is exact definition, which means diagnosis. On this Dr. C. V. Chapin, in 1910,

stated the position in respect to diphtheria very clearly. He said: "Many had long recognized that the diagnosis of diphtheria was difficult. It was suspected that many cases, because of this difficulty, escaped isolation entirely. When the culture method of diagnosis was devised, I became enthusiastic and hopeful. We adopted it in Providence in January, 1895, and soon after required a negative culture before the patient was released from isolation. Hill has shown that without cultures the chance of error in the diagnosis of diphtheria is 50 per cent., which corresponds entirely with my frequently expressed opinion before the advent of the culture method. It is evident, then, that the general use of cultures ought to bring to light great numbers of cases of diphtheria which were formerly unrecognized, and this it certainly does. If such an improvement in diagnosis, and consequently in isolation, is brought about by the use of cultures, and if by the same means isolation can be maintained until the patient is certainly free from infection, there ought to follow a marked reduction in this disease. But it was quite otherwise. The deaths in Providence, which in 1894 had numbered 45, rose to 79 in 1895 and 125 in 1896, nearly twice as many in proportion to the population as there were in 1883, when there was no isolation, no disinfection and no antitoxin. The cases rose from 166 in 1894 to 386 in 1895 and 890 in 1896. The apparent reduction in the fatality rate from 27.71 to 14.07 indicates very plainly that the culture method of diagnosis had discovered a very large number of mild cases that would have previously been unrecognized, for antitoxin was only a minor factor in reducing the fatality, as it had been used in only a little over one-third of the cases."

Other investigators have written in similar terms, and it must be recognized that accuracy of diagnosis has given rise to a false impression as to the effect of any system of treatment on the case mortality of present-day diphtheria when compared with the figures for the period from 1859 to the discovery of the bacillus of the disease. The question naturally arises whether any other factors have had a similar influence on the study of the problem.

Reference may be made to other diseases with which diphtheria is closely allied, viz., typhoid fever, measles, scarlet fever and whooping cough.

An Official Report of the State of Massachusetts deals with the results locally of the progress of preventive medicine. It gives the median and average number of deaths and death rates for the more prominent communicable diseases for the three ten-year periods 1890–99, 1900–09, and 1910–19. It says: "The statistics for the single year 1919 are given also to show that the deaths and death rates are still on the downward trend despite the increase in population. The common factors in the reduction of all diseases have been isolation of cases and quarantine of contacts.

The special factor in diphtheria which assisted in the lowering of the death rate is diphtheria antitoxin, introduced in 1894, and within a few years universally used. Prior to 1894, from 20 to 30 died out of every 100 ill with diphtheria, but in 1919 only 7 children died out of each 100 cases of diphtheria.

A remarkable fact in diphtheria fatality has been demonstrated in Paris and reported by Roux in the Office International d'Hygiène Publique, 1919, XI., No. 11. In the Children's Hospital in Paris there were 15,271 cases of diphtheria for the five years 1914–19. Of this number only 378 died, giving a fatality rate of 2.64 per cent. This indicates that the fatality rate of 7.2 per cent. for Massachusetts is still capable of being reduced."

Statistics relating to Massachusetts are given in the appended series of tables:—

POPULATION OF MASSACHUSETTS.

Year.	Population.	Year.	Population.
1890	2,238,943	1910	3,380,151
1900	2,805,346	1919	4,033,826

TYPHOID FEVER.

Period.	Deaths.		Death-rate (per 100,000).	
	Median.	Average.	Median.	Average.
1890–99	737	727	29.4	29.5
1900–09	518	501	16.6	16.7
1910–19	258	239	7.0	6.6
1919 (*a*)	..	..	..	..

(*a*) Deaths, 102 : death-rate, 2.6.

WHOOPING COUGH.

Period.	Deaths.		Death-rate (per 100,000).	
	Median.	Average.	Median.	Average.
1890–99	278	294	11.2	11.9
1900–09	269	303	8.3	10.1
1910–19	263	307	7.2	8.2
1919 (*a*)	..	..	..	..

(*a*) Deaths, 319 : death-rate, 7.6.

MEASLES.

Period.	Deaths.		Death-rate (per 100,000).	
	Median.	Average.	Median.	Average.
1890–99	127	155	5.2	6.3
1900–09	192	228	6.4	7.6
1910–19	263	278	7.6	7.4
1919 (*a*)	..	..	..	..

(*a*) Deaths, 183 : death-rate, 4.6.

SCARLET FEVER.

Period.	Deaths.		Death-rate (per 100,000).	
	Median.	Average.	Median.	Average.
1890–99	338	412	11.5	15.8
1900–09	299	284	10.0	9.9
1910–19	156	173	4.1	4.8
1919 (*a*)	..	..	..	..

(*a*) Deaths, 130 : death-rate, 3.3.

DIPHTHERIA.

Period.	Deaths.		Death-rate (per 100,000).	
	Median.	Average.	Median.	Average.
1890–99	1,440	1,413	60.3	57.6
1900–09	749	867	23.9	29.0
1910–19	627	638	17.1	17.3
1919 (*a*)	..	..	..	..

(*a*) Deaths, 591 : death-rate, 14.8.

From these tables it will be seen that in typhoid fever, whooping cough, scarlet fever, and diphtheria there has been a gradual reduction during the three ten-year periods. The case of measles is exceptional, and this has to be correlated with the fact that usually this disease is communicable by a sufferer to a healthy person for two or three days before any clinical symptoms are manifest (unless routine examination is made of the buccal cavity), whereas, in typhoid fever, whooping cough, and scarlet fever, a sufferer is usually obviously ill before being in a condition to infect another person. In the case of diphtheria, a reduction in the death-rate is manifest during the periods, but the reduction in scarlet fever is about the same in amount, and in typhoid fever is much greater. Had the diphtheria rate decreased as did that of typhoid fever, the average death-rate instead of being 17.3 would have been 12.8 only. The recorder states that "The factors common in the reduction of all diseases have been isolation of cases and quarantine of contacts," and then he says: "The special factor in diphtheria which assisted in the lowering of the death-rate is diphtheria antitoxin, introduced in 1894, and within a few years universally used." The death-rates from typhoid fever have fallen from 29.5 to 6.6 and from diphtheria from 57.6 to 17.3; and from the figures as stated there is nothing to show that any form of treatment was a special factor in the reduction that occurred, or was a factor in preventing the further reduction that might have been expected from the general common factors, viz., "isolation of cases and quarantine of contacts." In all investigations there is a danger of attaching too much importance to one factor to the exclusion of another, or of several.

In 1843 Sir Thomas Watson, in his lectures on "The Principles and Practice of Physic," wrote: "The exceeding value of statistical returns in determining the *causes* of disease has been admirably set forth by Dr. Alison; but, for directing the treatment of individual cases, it is far more profitable (as some one has well expressed it) to *watch* than to *count*. To use or to withhold a given remedy simply because it is found, by numerical calculation, that in cases nominally the same, recoveries have been more frequent when that remedy was employed on the one hand or omitted on the other, would be to sacrifice the plain and perhaps pressing indications of a particular case, to the statistical averages of diseases having merely a common denomination. To repeat what I have said elsewhere—we do not necessarily take the same symptoms as indications of treatment, which we trust to as signs of disease. We treat, indeed, not the so-called disease, but its accidents; the vital manifestations which proclaim its character and intensity, foreshow its tendencies, and illustrate its course."

It is an axiom in medicine that one cannot prescribe according to statistics. In any system of treatment, new or old, the manner of action of any agent or remedy demands most careful and critical study. No one can forecast what will prove to be essential and what accidental in its use, or what its effect will be in any particular direction. Examination, experiment, and logical induction alone can give trustworthy information.

In old times, wounds were healed through the introduction of the "Sympathetic Powder." Forty years ago the "carbolic spray" on the wound was regarded by many as the one essential in the new antiseptic system. Later on, neglect of antiseptic lavage of the post-partum uterus was characterised as almost a criminal proceeding.

A recent contribution will show the relative places of the essential and the accidental in producing results. Colonel Edward Munson, of the United States Army, writing in June, 1917, regarding an outbreak of measles among soldiers in a camp under his medical care, points out that, while his belief is that for measles any other disinfection than by

sun and air is unnecessary, he found that he was obliged to issue orders for the soldiers' clothing and equipment to be wetted by a chemical solution, in order to compel the men to spread the articles out in the sun and dry them before they were fit for use. Colonel Munson's experience was that neither officers nor men could be entrusted to carry out orders regarding simple disinfection by air and sun. There was a psychological necessity for the chemical solution.

On the subject of "professional statistics" Baginsky says: "The *value of statistics* in ascertaining the actual permanence of the processes and circumstances in things and in man is beyond all doubt and incontestable, and the less complicated the relations, the more certain and likely will be the results which may be determined from such a compilation, grouping, and addition. On the other hand, the scientific and conscientious statistician knows that on account of the complicating circumstances and relations attending figures, the difficulty of their proper estimation grows, and the results may be far from the actual truth. What can be more complicated than the course of morbid processes in which certain positive factors as to age, weight, social position, the number of affections, etc., are taken into account, but where innumerable other conditions that cannot be mentioned, even unknown circumstances, such as the constitution of the patient, the nature and virulence of the pathogenic agent, the favourable influence of remedies and of physician, as well as faulty observation and reports, and errors in treatment, may also affect the individual case. This renders professional statistics untrustworthy, and in so far as the most simple relations of figures are not taken into calculation, they are faulty, without value, and harmful." He adds: "Only after a very large, almost enormous number of results which include the omissions and errors of individual numbers are observed, is a result attained which approximates the truth. This, above all, renders general statistical reports regarding therapeutic results valueless, and so much inferior to the experience of the faithful observer who notes the minutest details. Hence the useless and detrimental controversy with statistically produced small figures regarding the curative properties of serum therapy. Are the conditions of a single region similar to those of another, or is even one case exactly like another, and even in the same places, under the same physicians, persons, conditions, are the morbid processes exactly similar? Do we not even see in this hospital how the severity of the individual case varies, the children coming to us having entirely different constitutions, their disease and a thousand other conditions varying greatly? But just for this reason the observation of an impartial well-trained physician who watches with open eyes is more valuable than all statistical reports. From this viewpoint, the judgment of serum therapy arising from careful clinical observations of the special case, with all the variations and surrounding conditions, is the only proper one, and the one that comes nearest the truth. This is the reason why we do not turn to the right nor to the left, but singly and alone, holding to our own base of observation, we arrive at our conclusions regarding the curative value of serum therapy, and shall even attain better results."

When the problem comes to be considered in detail one finds that various factors influence the incidence and the death-rate, such as the fallacies arising from inaccurate diagnosis and the inclusion of non-clinical cases of "carriers," and in this connexion one must remember that without cultures—which was the position before Behring's discovery—the chance of error in the diagnosis was said to be 50 per cent. This is a disturbing factor in all statistics before 1883 and for some time after, and it affects all comparisons made between the present and the past in respect to incidence and case-mortality. That it does so, is undoubted. Dr. Herringham, in Allbutt's System of Medicine, says that "since the diagnosis has been supplemented by the bacteriological test there is no question that if every patient is said to have diphtheria in whose throat the bacillus diphtheriæ is found, the average severity of the cases will diminish, since many such are, and remain, perfectly well, and would not have been so diagnosed in former times. In comparing statistics, therefore, it is necessary to be certain that the diagnosis rests upon the same grounds in all." So far, when making comparisons, it does not appear that any co-efficient of correction has been worked out, or even any allowance made for errors in the diagnoses previous to Behring's discovery.

(iii) *Influence of Age.* It has often been noted that age has a remarkable effect on the incidence and virulence of diphtheria; but the importance of this in statistics, especially in comparative statistics, has been but little noted.

In the Year-Book for 1859 figures are given from Ballard's investigations. His percentages show the number of deaths per hundred, not of cases but of fatalities.

DIPHTHERIA.—DEATHS IN AGE GROUPS, BALLARD'S INVESTIGATIONS.

Age Group.	Deaths.	Per cent.
Years—		
Under 1 ..	5	6.25
1–2	12	15.00
2–3	11	13.75
3–4	13	16.25
4–5	7	8.75
5–10	19	23.75
10–20	7	8.75
20	6	7.50

Summarizing the figures given above yields the following result :—

Age Group.	Deaths.	Per cent.
Years—		
0–5	48	60.00
5–10	19	23.75
Above 10 ..	13	16.25

The numbers involved here are as small as they are in most other similar compilations, but they all point to a distinct difference of fatality in respect to age. The " age periods " that are of most importance for comparison are from 1–5 years, from 5–10, and above 10. For a long time after 1859 it was noted that the 1 to 5 years period showed the largest number of deaths.

It is interesting to consider the causes of death in these cases recorded in 1859. They are set forth thus :—

DIPHTHERIA.—CAUSES OF DEATH, BALLARD'S INVESTIGATIONS.

Cause.	Under 5 Years.	Under 10 Years.	10 Years and upwards.	Period during which death occurred.			
				1 Week.	2 Weeks.	3 Weeks.	4 Weeks.
Laryngeal Affection	17	7	3	18	8	1	..
Exhaustion ..	13	5	4	7	8	3	4

Commenting on this matter Dr. Squire says in "Reynolds' System of Medicine" : " In diphtheria both local and general means of treatment are required ; the cure of particular cases may sometimes be attributable to the one and sometimes to the other, but in no case can either be safely disregarded. The general therapeutical indications are of primary importance throughout ; they consist neither in attempts to nullify a poison by specifics, nor to expel it by elimination, but in withstanding the encroachment of the disease, and in sustaining the vital powers."

Many series of statistics are now available, and they show that the increased tendency in many, if not most places, is for cases to be transferred from the first or more fatal group to the second or less fatal. The effect of such transference on the conclusions to be drawn from mortality statistics should be evident.

The following table shows the numbers of deaths from diphtheria in South Australia from 1888 to 1920, and their distribution in two groups—under 5 years and 5 years and over. The " transference " of deaths from the first to the second group commenced in 1897–1898, and it is remarkable as regards quantity. During the ten years in the first period, the percentages of the groups were 54.7 and 45.3 ; during the twenty-three years in the second period, the percentages were 45.8 and 54.2. It would be well if the incidence of the disease, *i.e.*, the number of cases notified in the various years were obtainable from

large series of statistics. These would furnish by far the most accurate and valuable information on the subject of the influence of the age periods.

DIPHTHERIA.—DEATHS IN AGE GROUPS. SOUTH AUSTRALIA, 1888 TO 1920.

Year.	Total Deaths.	Under 5 Years.	5 Years and Over.
1888	139	76	63
1889	109	63	46
1890	174	91	83
1891	173	94	79
1892	106	52	54
1893	100	50	50
1894	97	58	39
1895	37	21	16
1896	21	14	7
1897	22	16	6
1898	38	17	21
1899	40	19	21
1900	32	16	16
1901	19	9	10
1902	27	11	16
1903	21	8	13
1904	18	6	12
1905	7	2	5
1906	12	7	5
1907	13	9	4
1908	8	4	4
1909	14	4	10
1910	40	21	19
1911	65	30	35
1912	58	28	30
1913	78	46	32
1914	57	18	39
1915	72	29	43
1916	144	62	82
1917	87	42	45
1918	86	44	42
1919	82	33	49
1920	87	41	46

The following table gives a summary with percentages of the two age-groups for the periods 1888–97 and 1898–1920, and shows a remarkable reversal of the incidence figures :—

DIPHTHERIA.—DEATHS IN AGE GROUPS, SOUTH AUSTRALIA, SUMMARY 1888 TO 1920.

Period.	Total Deaths.	Under 5 Years.		5 Years and Over.	
		Total.	Per cent.	Total.	Per cent.
1888–1897 (10 years)	978	535	54.7	443	45.3
1898–1920 (23 years)	1,105	506	45.8	599	54.2

(iv) *Susceptibility.*—The " susceptibility " of individuals at various ages, and the relation of this to the mortality and fatality are extremely important factors. This is shown in the following table by Brownlee. He points out that the factors of infectivity and virulence are capable of existing in very different degrees of association. In this connexion the subject of exposure may become a very potent factor in the increase or decrease of mortality.

The accompanying table gives the figures for diphtheria taken from the returns of Manchester. Brownlee says these are chosen as they are the only returns where the actually notified cases and corresponding deaths are distributed in age periods.

DIPHTHERIA.—SUSCEPTIBILITY, MORTALITY, AND FATALITY, MANCHESTER, 1893 TO 1903.

Age Period.	Susceptibility.	Mortality.	Fatality.
Years—			Per cent.
0–1	89	62	69.6
1–2	271	160	59.0
2–3	293	152	51.9
3–4	392	161	41.7
4–5	356	129	36.2
5–6	325	100	30.8
6–7	199	56	28.1
7–8	187	44	23.5
8–9	152	34	22.4
9–10	124	14	11.3
10–15	74	5	6.8
15–20	46	2.1	4.6
20–25	37	1.1	3.0
25–35	29	2.5	8.6
35–45	16	.6	3.8
45–55	9	.4	4.4
55–65	5	..	..

New aspects of susceptibility and immunity have been presented within the past few years. Various factors may contribute to immunity. Immunity would appear to be inherent in some races or persons. The immunity that a person acquires by an attack of the disease may be called a pathological immunity.

Digby, in " Immunity in Health, 1919," says : " It is an arresting fact in medicine that some degree of immunity may be acquired by mere contact with cases of an infectious disease without an obvious attack. This may be called healthily-acquired immunity." Sir James Paget had noted this in 1871 when recording his personal experience of immunity from *post-mortem* infection and the result of his lapse from this acquired insusceptibility. Many surgeons have noted how well town-bred youths bear surgical operations, and how fast they improve during convalescence compared with country-bred subjects in the same wards ; and this is observed also in " medical cases."

Colonel Vaughan and Captain Palmer, of the United States Army, undertook an investigation for the purpose of ascertaining why the seasoned soldier is more resistant even to newly-imported infections than the recent recruit, why the men from crowded cities resist these infections transmitted from and to the respiratory tract more successfully than their comrades from sparsely settled areas, and why the rurals fall more ready victims to pneumonia than the urbans. After a critical review of clinical, bacteriological, and epidemic investigations, they said in " The Military Surgeon, 1920," " that the man who has been long accustomed to crowd life, and who has consequently frequently inhaled particulate proteins (bacteria), whether they be pathogenic or non-pathogenic, acquires a non-specific immunity, which helps him in withstanding infection." They point out that this conforms with some of the findings of the Typhoid Commission in 1898, contrary to the beliefs of the members when they began their investigations.

Another important factor must also be considered. Bodley Scott, in " Endocrine Therapeutics, 1922," writes : " It has been proved in human and in animal life that milk is capable of conveying antitoxin substances to the offspring after these have been injected into the mother ; this is transmitted immunity, but what is far more important is inherited immunity. Probably all infectious diseases in a civilized people eventually lead to a condition of partial and increasing immunity. This takes place partly *in utero*, but largely through the mother's milk during the first year of the child's life. In

artificially-fed babies this latter immunity-giving power is, of course, absent, and such are far more vulnerable to outside attack."

It may be that age-insusceptibility is co-related with maternal feeding from birth, with exposure to infectious diseases without acquiring them, and with complete recovery from some one or more of such diseases, but statistics on the subject are not available. An examination of susceptibility tables would seem to support the suggestion.

It is of interest in this connexion to note that the London notifications for 1892 to 1912 showed that one-third of the cases of diphtheria were under five years of age, about another third between five and ten, and for each succeeding quinquennium much smaller. The case-mortality was highest in infants under one year. This contrasts strikingly with Ballard's statement in 1859, that "the disease was comparatively rarely fatal to infants in their first year." This was at a time when breast-feeding was the rule.

The reference to food suggests another line of study and investigation. Rendle Short (1922), in a search for a cause in the increase of appendicitis, made a physiological, pathological, and food economic investigation, and found most support for the theory that the increase was due to the use of imported food-stuffs leading to a reduction in the relative quantity of cellulose consumed in the diet. He says, amongst other evidence: "The time-factor is correct. It was between 1895 and 1905 that the foreigner began to feed us, and that we imported appendicitis with his food. Since then, there has been little change in either." In the light of the physiological and pathological facts largely applicable to both diseases, and if the time-factor is correct for diphtheria as for appendicitis, one might find support for the suggestion that a liability to disease arising from diminished powers of resistance on account of lack of proper food elements was at least a possible factor in the increased susceptibility to diphtheria.

The term subepithelial lymphatics has been applied to certain glands in the body, viz., the faucial, lingual, and nasopharyngeal tonsils; the solitary lymphatic nodules of the intestinal tract; Peyer's patches; and the vermiform appendix. In their anatomy, physiology, and pathology, they are closely allied. Digby (1919) says their time of greatest activity corresponds with the period during which the individual is securing immunity against the exanthemata and other infections, and apparently one must correlate these two phenomena—the acquirement of immunity, and the activity of the glands. This activity is exhibited in the attack of scarlet fever, typhoid fever, appendicitis, and diphtheria. In diphtheria, the faucial tonsils are the special defensive organs, the biological barriers against invasion, and they become the portals of entrance of the specific poison when their protective powers fail. The vulnerability of an individual to infective disease is increased by the quality of the food, by functional impairment of the tonsils from recent attack of measles or similar disease, and by surgical removal of the tonsils. Tonsillotomy, it may be noted, began to be a common if not a fashionable operation about 1890.

(v) *Sex.* A table giving age and sex incidence of diphtheria for the County of London during the decennium ending 1903 has been given on an earlier page of this article. The figures in that table may be thus summarized:—

DIPHTHERIA.—DEATHS IN AGE-GROUPS, COUNTY OF LONDON, 1894 TO 1903.

SUMMARY I.

Ages.	Cases Notified.		Deaths.		Percentage Fatality.	
	Males.	Females.	Males.	Females.	Males.	Females.
Years—						
0– 5 ..	23,184	22,083	6,407	6,256	27.6	28.3
5–10 ..	16,854	20,328	2,110	2,692	12.5	13.2
10–15 ..	5,865	7,753	309	341	5.3	4.4
Above 15 ..	7,768	13,726	233	303	3.0	2.2

SUMMARY II.—COMBINED SEXES.

Ages.	Cases Notified.	Deaths.	Percentage Fatality.
Years—			
0– 5	45,267	12,663	27.97
5–10	37,182	4,802	12.91
10–15	13,618	650	4.77
Above 15	21,494	536	2.49

The abstracts made show the percentage case mortality in the two groups referred to, and would point to the same conclusion as one would draw from Ballard's statistics, though the two sets are not compiled in uniform fashion. Many series of statistics are now available; and they show that the increased tendency in many, if not most, places is for cases to be transferred from the first or more severe group to the second or milder group. Since the recoveries in this second group are more numerous, the effect of this on the conclusions to be drawn will be evident. Herringham, in "Allbutt's System of Medicine, 1905," when dealing with statistics, points out that the treatment elsewhere is not so uniformly successful as it is in London, and says: "It is not to be expected that it should be. Not only are the Board Hospitals magnificently equipped and maintained, but also, as it seems, both the public and the practitioners of London co-operate more promptly with the sanitary authorities than is the case in many towns. This is shown by the early date at which in London the cases are admitted to hospital;" and he draws a contrast between this and the defective administration in Manchester. It does not appear that this recently-introduced extensive and effective organization is estimated by any one as a factor influencing the diphtheria mortality when comparing present and recent statistics with figures of 30 years ago. It may be of interest, however, to note that the existence of legal powers and the commencement of administrative health activity in the control of the various infectious diseases, and the provision for what is universally recognized as the prime and specific necessity for saving life in diphtheria, viz., early treatment, coincided with the introduction and use of antitoxin.

(vi) *Urban and Rural Incidence.* Allbutt's "System of Medicine" states:—"The following table which relates to the quinquennium ended with 1903, shows the varying incidence of mortality from diphtheria and croup in town and country. The figures represent averag annual rates per thousand children living under five years, at which age diphtheria is more fatal than at other stages of life.

DIPHTHERIA AND CROUP.—DEATH RATES PER 1,000 CHILDREN LIVING, AGE GROUP UNDER FIVE YEARS—ENGLAND, 1899 TO 1903.

Sex.	Urban Counties.	Rural Counties.
Boys	1.86	0.96
Girls	1.79	0.92
Both Sexes	1.83	0.94

These figures indicate that in recent years the mortality from diphtheria has been much greater in the town than in the country—a distribution which is the opposite of that obtaining in the earlier years of civil registration, when diphtheria was commonly considered to be mainly a disease of the country. It is more than likely that the present excessive fatality of this disease—as well as of most other infectious diseases—in the urban areas is caused by the closer aggregation therein of school children as compared with rural areas. This rural to urban influx is a factor which deserves most careful study. It occurs in many countries. In Australia especially has it to be reckoned with, the massing of population in and around the capitals being proportionately greater than in any other part of the world. The facilities for the transference of infective material by carriers are enormously increased, not only on account of travelling, crowding and over-crowding in conveyances, of aggregations in schools and places of amusement,

but of "improvements" in sanitation in such matters as the providing of toilet requisities which, though good in theory, fail in practice because their insufficiency makes them adjuvants of infection instead of preventives.

(vii) *Influence of Antitoxin.* At the beginning of the antitoxin treatment a committee of the Paris Academy of Medicine reported: "We are now in possession of a specific treatment of diphtheria as powerful as it is harmless." If this meant that complications from the use of antitoxin did not occur, the statement has been belied on every hand. If it meant that it "cured" in every case, experience of the fatality rate is outstanding proof to the contrary. Unfortunately the statement gave rise to a belief that all failures or untoward results were to be explained away or concealed by imperfect and misleading statistics. The test of the comparative efficacy or relative utility of antitoxin must be its effect in every case or every class of case in which it is administered, as compared with other methods under similar conditions; while its absolute utility must be judged by the part it plays in the incidence and mortality of the disease in the general community—a subject which has received little or no attention. It is imperative, then, that in estimating its place and power one should carefully examine the statistics from which inferences have been drawn. In 1895 Sir Malcolm Morris, in "The Practitioner," after referring to the enthusiasm and contradiction that were being exhibited, and warning against statistical fallacies, wrote: "Let us, however, be quite clear as to what antitoxin can, and what it cannot, do. It is essentially an antidote to a specific poison; that is to say, it can neutralize the action of the poison, but it has no effect on the organic changes and functional disturbances caused by the poison. If used in time, antitoxin may, with tolerable confidence, be expected to prevent the occurrence of such changes and disturbances, but it cannot cure them . . . Nor must it be imagined that the antitoxin is an unfailing specific."

In an article in Allbutt's "System of Medicine" the following occurs: "It might be thought that there would be little difficulty in determining whether the antitoxin treatment is successful or not, for it means a simple matter by comparing records to decide whether the fatality of diphtheria is lower when antitoxin is given than when it is not. But it soon becomes clear that for various reasons and in various ways this simple test may prove fallacious. In the first place, since the use of antitoxin has now become universal in hospitals, it is seldom possible to compare two large series of cases treated at the same place at the same time, the one with antitoxin, the other without. There are, however, a few instances in which such a comparison can be made."

The writer, in the course of the article, says: "At the Blegdam Hospital in Copenhagen, Fibiger, under Sorensen's direction, divided cases merely according to the day of admission, treating with serum those admitted on alternate days, while those admitted on the intermediate days were treated without it. The experiment lasted from 13th May, 1896, to 13th May, 1897, and was carried out as arranged, except that toward its close the physicians, who were already driven to the conclusion that the serum had a powerful effect, used it on a few severe cases out of their proper turn. Excluding cases admitted moribund, which died within 24 hours, 483 cases in all were treated, as follows:—

238 with serum, of which 7 died, or 2.94 per cent.
245 without serum, of which 30 died, or 12.2 per cent.

Total 483.

Of the 238 cases treated with serum—
203 were pharyngeal, of which 4 died, or 2 per cent.
35 were laryngeal, of which 3 died, or 8.57 per cent.

Of the 245 cases treated without serum—
200 were pharyngeal, of which 14 died, or 7 per cent.
45 were laryngeal, of which 16 died, or 36 per cent.

Of the 238 cases treated with serum—
72 had albuminuria.
37 had paralysis.

Of the 245 cases treated without serum—
75 had albuminuria.
36 had paralysis.

It would hardly be possible to find two sets of cases more strictly parallel than these. The total death-rates are small as compared with those of other hospitals because they are calculated without the 'moribund cases,' which always form a large proportion of the total deaths. In both Baginsky's and Fibiger's cases the clinical diagnosis was confirmed by bacteriological investigation."

Besides the smallness of the total death-rates as compared with those of other hospitals, and the exclusion of moribund cases, there are serious defects—the writer omits all reference to the age-incidence, the time at which the various cases came under treatment, and other circumstances which have been proved to be of paramount importance in testing the efficacy of any remedy employed in treatment. One gathers no idea of what "treated without serum" implies. The record he quotes is obviously an example of what Dr. Baginsky has characterized as "professional statistics."

In many cases, the records appear to have their value enhanced by the statement that in all "the diagnosis was controlled by the bacteriological examination"—the writers apparently overlooking the fact that the effect of such diagnosis has been to swell the number by admitting cases that would not have been included in records with which comparison is made.

In the early days of antitoxin, when Katz reported on the treatment in Baginsky's wards, he stated that "the ordinary treatment by sprays, insufflations, etc., was carried on as formerly, and tracheotomy and intubation done when indicated. The cases were grouped into four classes: (*a*) slight, where the constitutional symptoms are absent or slight, and the membrane is restricted; (*b*) moderately severe, in which the throat is extensively covered and the glands affected; (*c*) very severe, when the nose and other parts are involved, and the general symptoms grave; and (*d*) cases to which septic processes are superadded. Of the first class, there were 47 cases, which all recovered; of 35 of the second, 1 died; the third class had 42, of which 31 recovered and 11 died; while the 4 septic cases all died."

This method of study is much more likely to give indications of the therapeutic value and place of any remedy than the wholesale or indiscriminate use of it without any means of discovering and setting forth accurate information. An examination of all the convalescents with a view to discover the number of carriers relatively to other series without local treatment might have yielded interesting results.

It has been said that the first axiom in the treatment of diphtheria is that there is no specific, that in no other disease are the individualizing powers of the physician tested more severely. Such individualizing powers have been shown in the experiments made by Lennox Browne in a series of cases, and his logical conclusions are noteworthy; but such records are conspicuous by their rarity.

In some records, embracing varied numbers of cases, one finds attempts at classifying the cases and estimating values of methods of treatment by accurate observation and judicious inference; but few recognize that the prime requisite for accurate evaluation is a true control series.

Herringham, in "Allbutt's System" says: "It is unsafe to compare strictly the hospitals of one town with those of another. There may be in their circumstances a difference sufficient to account for a difference in their death-rate. And even in comparing the past with the present rate of one hospital or group of hospitals, it is essential to be certain that there has been no great change in buildings, nursing, or medical attendance during the years included."

A report dealing with Massachusetts about 1919, states: "Sudden death occurred in 5.2 per cent. of the cases. In many instances lack of nursing care was the responsible factor. Another factor in the sudden death group appeared to be the repeated attempts at intubation where, for some reason, the tube was either not properly introduced or else expelled."

In the Medical Annual for 1897 it is recorded: "In connexion with the anti-toxin of diphtheria an important report was published at the beginning of the year—the joint production of the medical superintendents of the various hospitals of the Metropolitan Asylums Board—dealing with the diphtheria cases treated with antitoxin during 1895, and compared with those of 1894—the two years being comparable as to diphtheria

(severity, etc.)." Allowing for the "personal equation" of the various superintendents, the following results may be tabulated as proved from this Report :—

(1) Great reduction in the mortality of cases brought under treatment on the first or second day of illness, such reduction being specially marked in the laryngeal cases.

(2) Improvement in the results of tracheotomy.

(3) The clinical course of the disease slightly improved, as shown by the statistics, *i.e.*, in 1894, 3,042 cases and 902 deaths; 29.6 per cent. mortality; in 1895, 2,182 cases and 615 deaths, 28.1 per cent. mortality (46.4 per cent. of the cases treated being under five years of age).

(4) The earlier the treatment with antitoxin, the better are the results, *e.g.* :—

ANTITOXIN.—RESULTS OF TREATMENT, 1894 AND 1895.

Treatment.	1895 (Antitoxin).	1894 (All Cases).
Treatment commenced on 1st day ..	11.7% death rate ..	22.5%
,, ,, ,, 2nd ,, ...	12.5% ,, ..	27.0%
,, ,, ,, 3rd ,, ...	22.0% ,, ..	29.4%
,, ,, ,, 4th ,, ...	25.1% ,, ..	31.6%
,, ,, ,, 5th ,, ...	27.1% ,, ..	30.8%

It is noticeable that here a comparison is made between different years; that one set of death-rates refers to antitoxin cases alone, the other not to non-antitoxin cases alone, but to all cases, a method which is obviously defective. It would appear that the earlier treatment with antitoxin is credited with the improvements in the results, despite the fact that from 1859 onwards early treatment, apart from any particular method, was recognized as the great factor making for recovery.

In the Medical Annual for 1898 there is an article which follows up the above and adds the figures for 1896. The writer says: "The importance, however, of the antitoxin treatment is shown in a valuable (second) Report signed by eight (out of nine) medical superintendents of the various hospitals of the Metropolitan Asylums Board, and published during the year, giving an account of the use of antitoxin serum in the treatment of diphtheria during 1896 (*vide* also Medical Annual, 1897, p. 624). Of the total cases, 71.3 per cent. have been treated with antitoxin with the following results—to which are added, for comparison, the cases treated in 1895 (also partly with antitoxin), and those in 1894 (without antitoxin) :—"

ANTITOXIN.—RESULTS OF TREATMENT, 1894 TO 1896.

Day of Disease on which Treatment was Commenced.	Mortality per cent.				
	1896.		1895.		1894.
	All Cases.	Antitoxin Cases.	All Cases.	Antitoxin Cases.	All Cases, No Antitoxin.
First Day	4.7	5.2	11.7	4.6	22.5
Second Day	12.8	15.0	12.5	14.8	27.0
Third Day	17.7	21.9	22.0	26.2	29.4
Fourth Day	22.5	27.8	25.1	33.1	31.6
Fifth Day and after	24.6	31.7	27.1	35.7	30.8
Total	20.8	25.9	22.5	28.1	29.6
Tracheotomy Cases	41.0	40.6	..	..	70.4
Laryngeal Cases	29.6	28.8	..	..	62.0
Post-Scarlatinal Diphtheria ..	5.0	5.9	..	..	..

The same logical fallacies are evident here as in the former report.

Some examples may be given of statistics recorded in generally accepted authoritative works on the subject of diphtheria. The following is extracted from an article by Dr. Goodall in the second edition of the Encyclopædia Medica : " Before we proceed to discuss the question of the usage of the serum in the human subject we must draw attention to one very important point in the experimental evidence. It has been found that if an interval be allowed to elapse between the injection of the toxin, and subsequently the antitoxin, into a susceptible animal, then the longer the interval the less effectual will be the action of the antitoxin, and, finally, there comes an occasion when the interval has been made too long, and the antitoxin is injected too late to prevent the lethal effects of the toxin." Hence, it was predicted by Behring that the success of the treatment would be found to depend very largely upon the earliness of its application. Clinical evidence has amply borne out this prediction. The following figures, illustrative of this point, are taken from the Statistical Reports of the Metropolitan Asylums Board :—

ANTITOXIN AND NON-ANTITOXIN TREATMENT, 1894 TO 1897.

Day of disease upon which patient was admitted (1894) or brought under antitoxin treatment (1895–97).(a)	1st.	2nd.	3rd.	4th.	5th and later.
Non-antitoxin cases, 1894 ; all the hospitals—					
Cases	133	539	652	566	1152
Deaths	30	146	192	179	355
Mortality	22.5	27.0	29.4	31.6	30.8
Antitoxin cases, all the hospitals (1895–96) ; with Brook and Eastern Hospitals only for 1897—					
Cases	209	1126	1313	1332	2436
Deaths	8	137	275	376	780
Mortality	3·8	12·1	20·9	28·2	32·0

(a) No further statistics illustrative of this point and relating to all the hospitals were published by the Asylums Board till the year 1911. It was found that for that year the mortality for each day was as follows :—1st, 2.6 ; 2nd, 3.4 ; 3rd, 8.9 ; 4th, 12.5 ; 5th and later, 13.4. These figures related to 3,864 cases.

The 1894 figures refer to the day of the disease on which the patient was admitted, and to all the hospitals, and to non-antitoxin cases. The figures for 1895–96 refer to the day on which the patient was brought under antitoxin treatment, and to all hospitals, with Brook and Eastern Hospitals only for 1897. In view of the number of conditions which must be considered in estimating the place and power of any factor in treatment, these statistics are not such as to furnish accurate conclusions to the statistician. And yet these statistics of the Metropolitan Asylums Board are received and quoted as the most trustworthy on the subject.

(viii) *Summary of Present Position.*—In the Medical Annual for 1901 reference is made to a statistical study (locality not mentioned) by Dr. J. E. Herman, in these terms : " In view of the fact that in late years there has been a decline in the death-rate of other infectious diseases than diphtheria, against which no new remedy has been directed, he announces the failure of antitoxin in the treatment of diphtheria."

The article then states that Dr. William P. Munn reaches a different conclusion, founded on statistics of antitoxin treatment in Denver, Col., during five years 1895–1899, in which Denver had almost half as many cases of diphtheria as during six preceding years, but with one-sixth as many deaths from the disease.

The following occurs in the U.S. Public Health Reports, Vol. 34, No. 20 : " In their weekly Bulletin of March 15, the New York authorities call attention to the fact that, although there had been a continuous reduction in the death rate from diphtheria, ' the mortality from this disease is still much higher than it should be, when we consider the armamentarium at hand for preventive and curative work.' In New York City, despite

the excellent results of antitoxin treatment, diphtheria still causes over 1,000 deaths annually, approximately 20 per 100,000 population. Rates only a little less than this prevail in Rhode Island, Pennsylvania, Kentucky, North Carolina, Massachusetts, and Michigan." It is pointed out that during the period 1891 to 1900 there were 17,845 deaths from diphtheria in the city of New York among persons under fifteen years of age, and 81.5 per cent. of these were under five, and that efforts to effect further reduction in diphtheria mortality should manifestly, therefore, be mainly centred on the latter age group. There is a recognition here that other factors than antitoxin are concerned in the reduction of mortality rates.

In 1907, Rubner called attention to the increasing incidence and malignity of diphtheria, his knowledge being gained by inquiry among German Medical Officers of Health. He says: "The result was that in our province, in the Empire, and also in the majority of the large towns and districts the disease is neither diminishing nor even stationary, but that an obvious and, in some districts, alarming increase is apparent; and the disease continued to show a manifest inclination to such an increase among us also, even as late as May, 1912. Nor can local causes for a spontaneous decline of diphtheria be discovered."

In Chicago, from 1912 to 1916 inclusive, 6,817 patients were admitted to the State Hospital. Of these 834 died—case mortality was approximately 12 per cent. The number of patients under treatment in 1916 was about 200 greater than in 1912, which indicates a marked increase in the prevalence of diphtheria in Chicago at that time. The recorder notes that few cases occurred in the coloured race, the negro being relatively immune to diphtheria.

Carey states in the Boston "Medical and Surgical Journal," 1919, that "with an average of 6,500 or more cases being reported yearly, with approximately a 10 per cent. fatality, we cannot in truth say that we are progressing with endemic diphtheria" . . .

These are examples that set forth the conditions that obtain generally throughout the world regarding the increase in incidence of diphtheria and the loss of life in various communities, a loss which is not decreasing, and which presents one of the most difficult problems in present-day medicine.

11. **Carriers.**—(i) *General.* The subject of the diphtheria carrier does not belong exclusively to the present day, nor does it date only from yesterday. It was recognized more than half a century ago. It is referred to by Dr. Squire in Reynolds' System of Medicine, 1866.

An individual may show the presence of diphtheria bacilli in his throat, and soon after may suffer from the disease. He is termed an "incubationary carrier." Another, who has recently recovered from the disease, may exhibit bacilli either constantly or intermittently. He is termed a "convalescent carrier." Persons who have been exposed to infection may show the constant or intermittent presence of bacilli without contracting the disease. Such are termed "contact carriers." The condition is explained by the supposition that the bodily state is such that it can resist the effects of the toxic material manufactured by the germs locally in the throat; and such resistance may continue temporarily or indefinitely. Without discussing the subject of the virulence or non-virulence of the bacilli in carriers, one may assume for administrative purposes that all persons with such "localized" bacilli are possible disseminators of disease. The healthiest looking carriers may spread germs of the most virulent sort. The question of what is to be done to prevent dissemination is perhaps the most pressing and the most difficult problem of the day connected with the control of diphtheria. Antitoxin, no matter how administered during or after recovery from the disease, has no effect on such bacilli.

The discovery of carriers is not difficult. Susceptible individuals may easily be discovered and presumably protected; and it might be thought that control would be easy. Henry J. Nichols, in "Carriers in Infectious Diseases, 1922," says, however, that practically the programme usually breaks down because it is too big; and he gives cogent reasons in support of his statement.

(ii) *Convalescent Carriers.* With convalescence, the bacilli begin gradually to disappear, and, by the end of a month, 85 per cent. of convalescents are bacteriological recoveries. By the end of a second month, 98 per cent. are free. The remainder pass into the most dangerous class of more or less chronic carriers.

(iii) *Contact Carriers.* Pure contact carriers occur among attendants, families, and contacts of cases, and carriers in from 10 to 20 per cent. of instances. The organisms are virulent in 80 per cent. of instances, and the carriers are dangerous, but the condition is temporary unless there is some predisposing deformity of a chronic focus. These carriers are immune or "Schick negative."

(iv) *Proportion of Carriers to Population.* In the general population, true carriers of virulent organisms are less than 1 in 1,000. Among children, however, 2 per cent. are true carriers. Only 10 per cent. of non-contact or non-convalescent carriers show virulent organisms. [The statements in (ii), (iii), and (iv) are made on the authority of Nichols.]

The following table by Chapin sets forth the results of an examination of all the wage earners in the families at the time the cases were reported, and of all the members of the family for release, that is, to determine the end of isolation. Chapin also gives statistics of a large number of examinations in schools in America, Great Britain, and the Continent of Europe.

DIPHTHERIA.—NUMBER AND PERCENTAGE OF CARRIERS, PROVIDENCE, U.S.A., 1897 TO 1901.

Ages.	Persons Examined.	Number of Carriers.	Percentage of Carriers.
Under 1 year	119	17	14.2
1 year	112	15	13.3
2 years	97	23	23.7
3 ,, ...	112	25	22.3
4 ,, ...	116	31	26.7
5 ,, ...	120	17	14.1
6 ,, ...	137	42	30.6
7 ,, ...	130	30	23.1
8 ,, ...	119	25	21.0
9 ,, ...	113	23	20.3
10 ,, ...	139	26	18.7
11 ,, ...	79	11	13.9
12 ,, ...	127	28	22.0
13 ,, ...	86	15	17.4
14 ,, ...	88	13	14.7
15 ,, ...	70	5	7.1
16 ,, ...	64	9	14.0
17 ,, ...	57	9	15.7
18 ,, ...	57	6	10.5
19 ,, ...	45	4	8.8
20 ,, ...	34	4	11.7
Adults	2,505	277	11.0
Totals	4,526	655	14.4

At the Fifteenth International Congress at Washington in 1912, Dr. W. Lorenzo Moss stated that the problems urgently demanding solution were: "1. May avirulent diphtheria bacilli become virulent, and under what conditions? 2. Under what conditions may virulent diphtheria bacilli cause clinical diphtheria? 3. How may the sterilization of diphtheria-bacillus carriers be accomplished?" He says that "until these problems have been solved, or, at least, until the solution of the third one has been accomplished, we are scarcely in a position to deal with the healthy diphtheria-bacillus carrier. This, of course, does not mean that the rigorous measures usually adopted against cases of clinical diphtheria should be relaxed."

(v) *Treatment of Carriers.* The isolation of "carriers" is allowed to be impracticable. The part they play in the spread of the disease, directly and indirectly, is becoming more and more recognized; and they are being regarded as a most important means of

conveying infection. The significance of this is obvious when one considers that in the social conditions of to-day a person may be more likely to spread infection to another country or continent than half a century ago he would have been liable to infect a person in the next parish.

There has been a good deal of investigation into the carrier question both generally and experimentally by Shick-testing and immunizing with antitoxin, toxin-antitoxin, avirulent bacilli and other substances; but, although there has been much discussion, there is no consensus of opinion as to what administrative measures would be justifiable, practicable, or efficient in dealing with " carriers " in a general community.

(vi) *Place of Schools in the Control of Diphtheria.*—For a time the part played by schools in the dissemination of diphtheria was doubtful. It had been noted that the greatest number of deaths occurred among children under school age; but the question was raised whether these received the infection from school, or whether they were the source of the school infection. It was held that among older children the school played a large part in the spread of the disease. The facilities that a school gives for the spread or the check of an epidemic will depend largely on the amount of attention of a sufficiently skilled nature that can be given to the children both in school and at home, on the facilities for detection and isolation of sufferers, on the discovery and exclusion of carriers, and on prompt and effective measures of disinfection. Cities should be more favourably situated in respect to these matters than country places, but if precautions are neglected, the facilities for spread will, on the other hand, be so much the more multiplied. There have been so many opportunities of estimating the effects of varied experience in various classes of circumstances that there is not much difficulty in deciding what method will promise the best results in any given case—provided always that all the circumstances are known, and that all the measures recommended for control are promptly taken and minutely carried out.

(vii) *The Diphtheritic Membrane.* On a review of the clinical observations on the action of antitoxin, and statistical evidence on the subject, it would appear that the diphtheritic membrane may be the crux of the problem. The presence of the membrane has a twofold effect on the patient: (*a*) it makes the acts of breathing and swallowing difficult, and so interferes with respiration and nutrition; and (*b*) it exhausts the patient by the efforts made to resist the local applications for relief. Antitoxin, on the other hand, not only improves the general condition of the sufferer, but makes local applications unnecessary, or less necessary, and so conserves the patient's strength and at the same time allows the free administration of nourishment and stimulants. But, as contrasted with this, it has no effect on the presence of the bacilli in the throat during or after convalescence, and so allows the patient to remain in a condition to mingle freely with others, and to be a possible or actual cause of the spread of the disease. In the light of recent findings it would appear that local treatment of the membrane by destroying the bacilli had a double effect: it checked the supply of the toxin to the patient's system, and it prevented the spread of infection by the bacilli from the patient to others during and after the attack.

12. **The Problem of Eradication.**—About five years ago the Massachusetts State Department of Health made a statistical study of 1,000 deaths due to diphtheria in order to find the causes and, if possible, to remedy them, being " deeply concerned by the apparent apathy of physicians and organized health agencies towards the failure of the morbidity to decline, while the mortality rate has been so markedly reduced by the use of antitoxin." The private practitioner has no professional or pecuniary interest in the eradication of communicable disease. He is not a philanthropist. The officer of health and his employers as a corporate body may have such an interest if the expenses of control or eradication fall on them. But the interests of the family physician and the officer of health are not as yet identical or even similar. It is sometimes said that they are diverse or antithetical. Even commercial considerations of sorts are not entirely foreign to the diphtheria problem. If these things are so, it would not be an unwarranted inference that while antitoxin reduces the case mortality, it may be a powerful factor in the increased incidence of the disease. It should not be impossible, or even difficult, to conduct a series of test experiments that would furnish trustworthy information on this crucial question.